2H960SA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

410-009-0

In Re Application Of:	
NORBERT BUSCH ET AL	
Serial Number: 015,752	Group Art Unit 122
Filed: February 27, 1979	Examiner: TOVAR
For: AN ETHER OF N-PROPANOL AMINE	

DECLARATION UNDER 37 CFR 1.132

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

Sir:

Now comes Norbert Busch who declares and states:

1. I am the Norbert Busch who jointly with Roland-Yves Mauvernay, Jacques Simond, Andre Monteil and Jacques Meleyre made the invention which is described in United States Patent 3,962,238, issued on June 8, 1976.

2. I am the President of the Administration Board and Scientific Director of Centre Europeen de Recherches Mauvernay (hereinafter referred to as CERM) and I am authorized to make this declaration on behalf of that Company.

3. United States Patent 3,962,238, issued on June 8, 1976, describes the synthsis of certain propanolamines from already known amino alcohols by a two-stage procedure. The first stage involves the replacement of the hydroxyl group of these amino alcohols by a chlorine atom and the second stage involves reacting the resulting compound containing a chlorine atom with an alkali derivative of specified amines. The first stage is a straight forward reaction but the reaction of the second stage could proceed in more than one way and, after we had carried out the reaction, we carried out experiments to determine the structure of the products

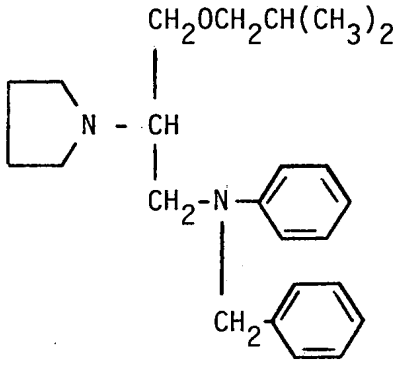
which we had obtained thus hoping to decide the way in which the reaction proceeded. On the basis of the information which we obtained from these experiments we drew up a general formula for the products and, when it had been shown that some of these products possessed interesting pharmacological properties, we proceeded to file a patent application in France on March 6, 1972 and, subsequently, a corresponding patent application was filed in the United States. At that time, we had no doubts as to the structure of the products which we had obtained.

4. Under the terms of an agreement which the Company had with an American firm, Carter-Wallace, Inc., we submitted information concerning one of the most interesting products, CERM 1978, to them and their interest led to a wish to carry out experiments on the metabolism and biodegradability. To do this, they needed a detailed synthesis of a labelled form of the compound. This information was transmitted to them in a letter dated July 6, 1976 sent to Dr. D. J. Wilkins of Carter-Wallace which described a synthesis using C^{14} - labelled materials. It transpired that this information was passed to a Dr. Reisner of Wallace Laboratories which is a division of Carter-Wallace, Inc.

5. We subsequently received a letter, dated August 6, 1976, in which we were informed that Dr. Reisner had questioned the structure assigned by us to the product CERM 1978 and asked what proof we had for the formula. This letter was accompanied by a memorandum from Dr. Reisner. Copies of this letter and the enclosure thereto constitute Exhibit A attached to this Declaration. From this time CERM and Wallace Laboratories independently carried out further experiments to obtain further information which would elucidate the structure of CERM 1978.

6. The most important line of approach available appeared to us to be to try to carry out an unambiguous synthesis leading to the compound

having the alternative possible structure to that postulated for CERM 1978, viz.



After about 4 months work, an unambiguous synthesis from ethyl α, β-dibromopropionate was successfully accomplished. Samples of this product and of the original CERM 1978 were submitted to the University of Paris for determination of the mass spectrographs of the compounds. Their report is dated January 10, 1977 and they reached the conclusion that the two samples were of the same compound and that both had the alternative structure set out above. This was the first definite evidence that we had obtained in favor of the alternative structure. A copy of the report of the University of Paris, and a certified translation thereof, constitute Exhibit B attached to the Declaration.

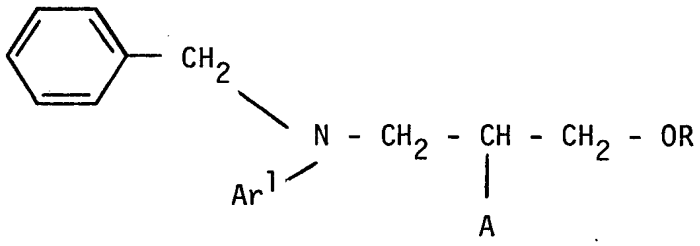
7. Whilst we were engaged upon the above work, Wallace Laboratories were carrying out experiments of their own devising. The results of these experiments were communicated to Mr. Houldsworth of CERM in a letter dated December 23, 1976 accompanied by a request that their findings be transmitted to me. These findings are summarized in a memorandum from Mr. F. J. Stiefel to Dr. Reisner dated December 15, 1976 and in a report to Carter-Wallace, Inc. from Shrader Analytical and Consulting Laboratories, Inc. who carried out a high resolution mass spectrographic examination of a compound therein referred to as RC-754 which, I am

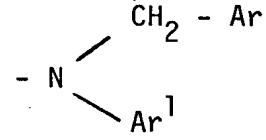
advised, is the same compound as CERM 1978. Copies of the memorandum dated December 15, 1976 and of the report from Shrader constitute Exhibits C and D attached to this Declaration.

8. With the various data thus accumulated in front of me, I drew up a document setting out (a) my review of the data submitted by Carter-Wallace and (b) my revised views upon the structure of CERM 1978 having regard to the unambiguous synthesis referred to above. The reasons which led us to assign an incorrect structure are also indicated in this document. A copy of this document constitutes Exhibit E attached to this Declaration.

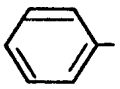
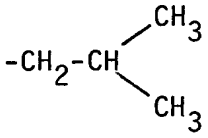
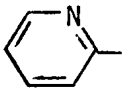
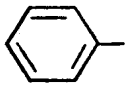
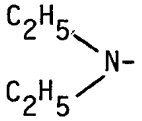
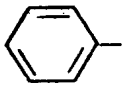
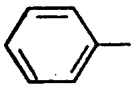
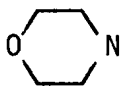
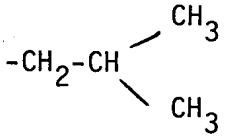
9. At this stage, I accepted that the available evidence indicated an incorrect structure had been assigned to CERM 1978 but we had no evidence concerning the other compounds described and claimed in U.S. Patent 3,962,238. It was therefore decided that additional quantities of certain other compounds described in U.S. Patent 3,962,238 must be synthesized and further work carried out to try and determine their structure. Since mass spectrography had proved the most direct way of obtaining information on the structure in the case of CERM 1978, samples of compounds CERM 1979, 1991, 3012 and 3080 (all of which appear in Table I of U.S. Patent 3,962,238) were submitted to the same laboratory of the University of Paris for their mass spectrographs to be determined.

10. The report subsequently produced by the University of Paris indicated that all possessed structures similar to the alternative possible structure postulated for CERM 1978 when due account was taken of the substituents present in the starting materials used to produce them. With this additional evidence available, it was clear that a similar phenomenon had occurred in the production of all of the compounds and accordingly that the correct general formula for the compounds is:



In effect this means that when compared with the original formula, the positions of the groups  and A have been interchanged.

11. The several compounds further investigated were:

Example in USP 3,962,238	House No. CERM	Ar^1	A	R
1	1978			
2	1979			ditto
3	1991			ditto
4	3012			$-CH_3$
5	3080			

12. A copy of the report received from the University of Paris dated July 11, 1977 and a certified translation thereof constitute Exhibit F attached to this Declaration. These results indicated that the isomerization which occurs in the production of CERM 1978 also occurs in the production of the other compounds listed above and accordingly the general

formula set forth above must be considered to be the correct general formula for all the products.

13. The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

14. Further Declarant Saith Not.

Date: April 28, 1980 Signature: Norbert Busch

CABINET
HARLÉ & LÉCHOPIEZ
INGÉNIEURS-CONSEILS EN PROPRIÉTÉ INDUSTRIELLE

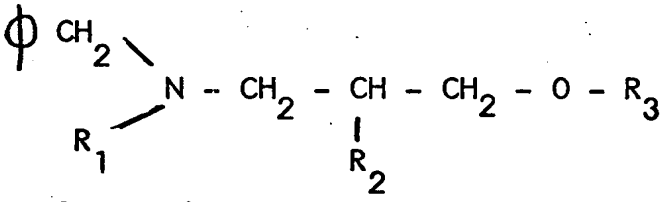
July 11, 1977

PARIS VII UNIVERSITY

Molecular drug chemistry Laboratory

MASS SPECTRA OF SAMPLES N°s 1979, 1991, 3012, 3080

Having the general structure:



1) Molecular peaks:

1979 : weak M^+, (367) and impurity at M = 391

1991 : M^+ inexistant (368), but presence of a peak at M= 372

3012 : weak M^+ (324)

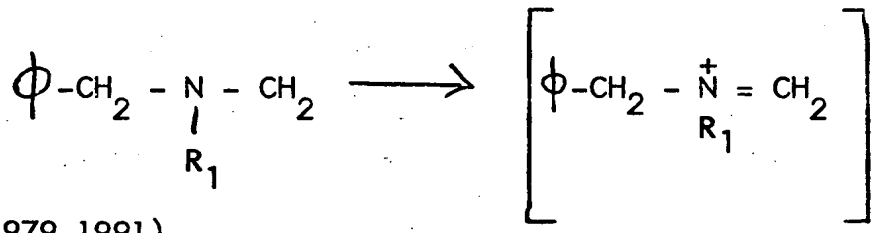
3080 : medium M^+ (382)

The small size of these peaks, and the fact that they do not exist for 1991, demonstrates the fragility of the molecules propoeed (source : 150°C energy 70eV).

The presence of a supplementary high mass peak is due to impurities.

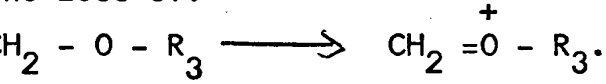
2) Fragmentations:

The most important fragmentation, which provides the basic peak in several cases, is the withdrawal of:



(1979, 1991).

Symmetrical fragmentation of the first is observed, corresponding to the loss of:



(1979, 1991, 3080).

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Finally, the 3rd type of fragmentation corresponds to the loss of:

$$R_2 - CH - CH_2 - O - R_3 \longrightarrow R_2 - \overset{+}{C}H - CH_2 - O - R_3$$

(3012,3080).

Then the breakdown of the various groups is very normally observed.

for R. MILCENT

J.J. GODFROID

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INGÉNIEURS-CONSEILS EN PROPRIÉTÉ INDUSTRIELLE

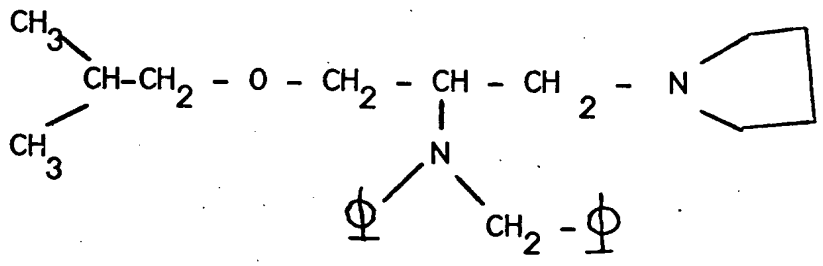
January 10, 1977

MASS SPECTROSCOPIC ANALYSIS OF SAMPLES

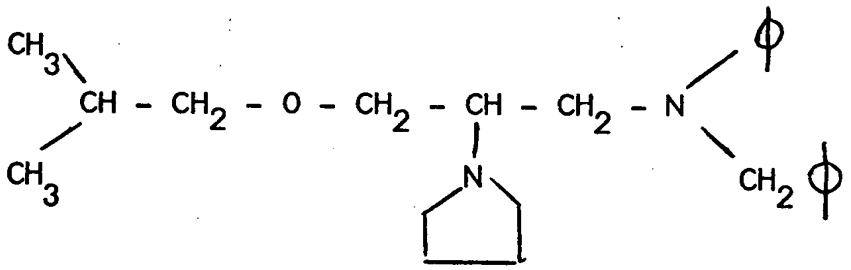
CERM 1

and CERM 2

Structure proposed for $CERM_1$:



Structure proposed for $CERM_2$:



The two spectra are, on the whole, identical, but the $CERM_2$ spectrum shows a few additional peaks of fairly considerable abundances: this concerns m/e : 290 , 241, 237, 142 and abundance peaks higher than those of the $CERM_1$ spectrum m/l : 222, 210, 208, 201. The first, to which it was impossible to attribute a formula, might arise from an impurity contained in sample $CERM_2$ (stained yellow). The second remains inexplicable unless the hypothesis of an experimental aberration is accepted.

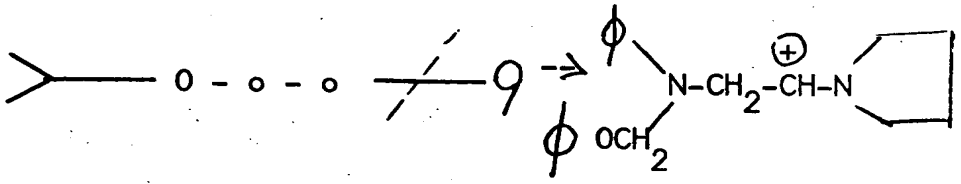
1st conclusion: both spectra correspond to one and the same product.

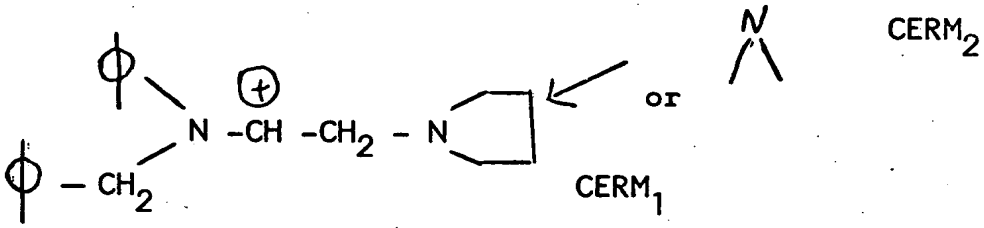
Study of some large abundance peaks of the two spectra:

m/e : 366 : molecular radical ion

m/e : 362 : 1 to 1 loss of 4H in the molecule.

m/e : 279 : rupture :

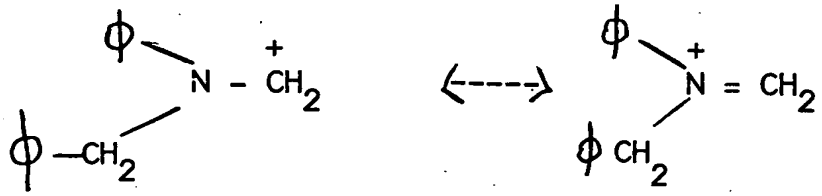




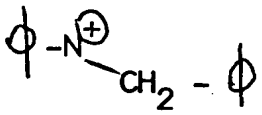
$CERM_2$

$CERM_1$

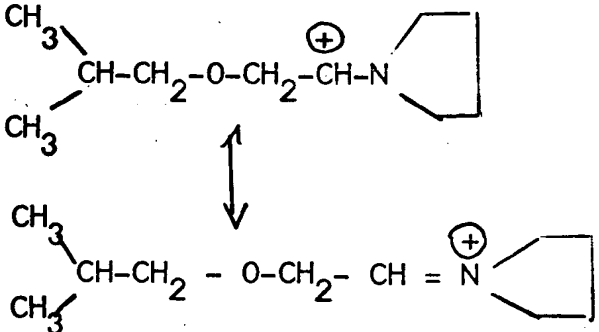
m/e : 196: corresponds to another possible rupture only possible for the $CERM_2$ structure of which 1 of the ions formed is:



m/e : 182 = :

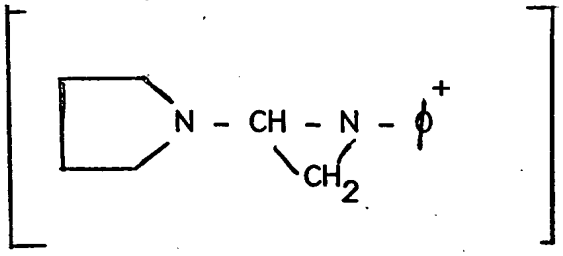


m/e : 170 : attributed to



characteristic of the structure $CERM_2$.

In case of the addition of m/e: 199, of weak abundance which can be attributed to



the results obtained make it possible to arrive at a second conclusion: the structure of the product is that of $CERM_2$.

Appeal No. 378-66 ljk

HEARD:
September 10, 1979

SEP 27 1979

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF APPEALS

Ex parte Leonardo Marsili,
Vittorio Rossetti
and
Carmine Pasqualucci

Application for Patent filed May 12, 1976, Serial No. 685,624. Novel Rifamycin Compounds of High Antibiotic Activity.

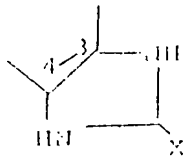
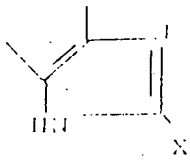
Norman F. Oblon et al. and Milton Sterman for Appellants.

Before Magil and Sturtevant, Examiners-in-Chief, and Rzucidlo, Acting Examiner-in-Chief.

Sturtevant, Examiner-in-Chief.

Appeal has been taken from the final rejection of only one claim, the generic product claim 1. A copy of this claim is attached as an Appendix hereto. All the remaining claims in the application have been allowed: claims 2, 3 and 4 directed to the method of making the compounds of claim 1, and claim 7 which defines the new compounds in product-by-process terms.

The sole issue before us is whether or not claim 1 contains new matter, which is prohibited by 35 USC 132, final sentence. The disputed "new matter" involves a change in the structural formulae for the product in the specification and in claim 1. The precise nature of this change is well expressed by the following excerpt from Appellants' Brief (page 4):

> "...appellants initially considered that the compounds they prepared contained the following imidazoline ring across the 3,4-position of the Rifamycin -SV type structure
>
> 
>
> see formula (I) as initially presented on page 1 of the specification (X is a defined substituent which may be hydrogen).
>
> Further, more refined, analytic investigation showed that the ring in fact was and is the imidazole ring, which is the stable aromatic structure:
>
> 
>
> An imidazoline is a dihydro-imidazole."

After a final rejection on other grounds, not now pertinent, Appellants filed an amendment to make the above changes. The amendment was at first refused entry as raising the issue of "new matter", the Examiner citing Ex parte Fox, 128 USPQ 157 (Bd. 1957). Subsequently an amendment making

the changes was again proffered together with a declaration by one of the Appellants providing both analytical data and literature references to support the propriety and scientific desirability of the changes. These papers the Examiner entered "in order to test the question of new matter before the Board of Appeals" (Paper No. 10, page 2). We congratulate the Examiner for taking this action, which brings this interesting question properly before us.

In the briefing of this issue a number of cases have been cited by counsel and the Examiner, besides the Fox case. After careful review of them and other case law, as well as the entire record, we conclude that the Examiner's rejection must be reversed. We do not believe that either the Fox case or another Board of Appeals case cited by him (Ex parte Davisson & Finlay, 133 USPQ 400; 1958) is in point. In both of those cases it was held that the original description of the claimed product was insufficient to identify it or distinguish it patentably from the prior art compounds. In other words, the product could only be distinguished from others in terms of the process of making it. Here we have the question of changing the original description of a product which is admittedly patentable and was described by sufficient characteristics to distinguish it. We do not here have the question of adding characteristics not previously mentioned.

Instead, we consider that a case cited by both Appellants and the Examiner, decided some years ago by the Court of Customs and Patent Appeals, and frequently cited and

followed since, remains a leading case on the question and dictates our reversal of the Examiner's decision. This case is In re Nathan et al., 51 CCPA 1059, 328 F.2d 1005, 140 USPQ 601 (1964)*. There the original disclosure merely identified certain steroid derivatives as containing a "2-halo" substituent and the issue was whether a subsequent amendment to define the substituent as alpha-oriented was new matter. There also, as here, Appellants submitted a showing under Rule 132 (now 37 CFR 1.132) to support the propriety of the change and to show that the alpha-orientation of the halogen was an inherent characteristic of the claimed compounds. The Court reversed the PTO, holding that the change had not introduced new matter but was "merely a statement of an inherent property of the steroids as disclosed in appellants' original disclosure" (51 CCPA 1062).

Two more recent CCPA decisions, which cite with approval the Nathan case, are in our opinion very much in point because of the closeness of their factual situations with the facts of the case now before us. These are In re Sulkowski, 487 F.2d 920, 180 USPQ 46 (CCPA 1973) and Spero v. Ringold, 54 CCPA 1407, 377 F.2d 652, 153 USPQ 726 (1967). In the Sulkowski case the parent application had identified the structure of the claimed compound as "3,4-dihydro-6-phenyl-2,5-benzodiazecin-1(2H)-one," whereas in the application on appeal it was identified as an isomer of that compound, namely "9B-phenyl-1,2,3,9B-tetrahydro-5H-imidazo [2,1-a] isoindol-5-one." The Examiner had refused to accord Appellant

* For the sake of completeness note also a much earlier leading case on this question, also frequently cited: Bierster v. Rendall, 34 CCPA 859, 159 F.2d 732, 72 USPQ 481 (1947)

the benefit of the filing date of the parent application because the error in the structure there given would not have been obvious to one of ordinary skill in the art. The Board of Appeals had affirmed the Examiner's decision but indicated that, if there had been timely filed proof that the claimed products inherently had the corrected formula, the Examiner's rejection would have been reversible. Citing Nathan and other decisions to the same effect, the CCPA remanded the Sulkowski case to the Board for consideration of such proof of inherency.

In Spero v. Ringold, an interference case also involving the right of one party to rely on the date of a parent application, in the Court's own words "...we have the anomalous situation presented that while the inventor may not have known the configuration of the compound produced by his process, an expert in the art testified that the compound necessarily has the predictable configuration which meets the count" (54 CCPA 1410). The Court, again on the basis of persuasive evidence that the product inherently had the corrected configuration, reversed the PTO and accorded the parent filing date to Spero. See also In re Hagerlein et al., 52 CCPA 1637, 346 F.2d 609, 145 USPQ 683 (1965) and In re Fisher, 57 CCPA 1099, 427 F.2d 833, 166 USPQ 18 (1970), both also holding that a structural formula may be corrected without violation of 35 USC 132, if "there is sufficient evidence in the record to show the (proposed structure) to be an inherent characteristic of the subject matter so identified" (In re Hagerlein et al., 52 CCPA 1640).

In the record now before us the declaration by one of the Appellants provides excerpts from the "specialized literature" demonstrating, in the words of the declarant, "that the structural formulae originally assigned to the compounds...had to be held uncorrect (sic)" (Paper No. 9, paragraph 9). The declarant also describes subsequent research by CMR spectrometry and provides the supporting chemical and physical data which, he avers, "have confirmed that the original structural formulae determination was in error" and support the accuracy of the formula correction (Paper No. 9 at paragraphs 11-13). We find this evidence persuasive and consider that the usual presumption of correctness of the data in an application as filed has in this instance been overcome, as to the structural formula of the claimed compounds, by the Marsili declaration evidence.

We conclude from this evidence, therefore, that the products described, exemplified and claimed by Appellants inherently had and have now the structure given in the amendment in question. Consequently, the changes made in this amendment do not constitute new matter.

In conclusion, we note a persuasive and logical point in Appellants' Reply Brief (page 2):

> "No one derives any benefit from an erroneous statement - neither applicants nor the public."

Also compelling in its logic is the observation by the CCPA in still another decision involving proper identification of new compounds (Petisi et al. v. Bernhard et al., 53 CCPA 1452, 363 F.2d 903, 150 USPQ 669; 1966):

"The *product*, not the formula or name, is the invention," (53 CCPA 1457)

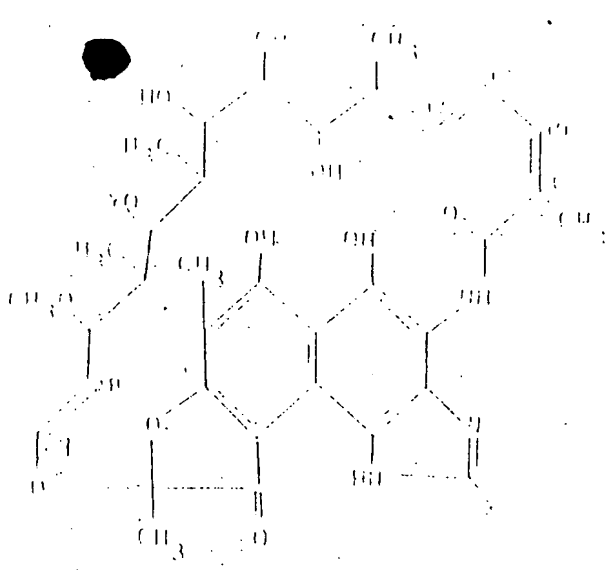
The PTO exists to carry out the job assigned it by Congress, pursuant to the Constitution (Article I, Section 8), i.e. to issue patents which "promote the Progress of Science and useful Arts." To refuse correction of the structural formula of Appellants' claimed compounds, which have been found patentable by the Examiner, would lead to the absurdity of issuing a patent which teaches the public in its specification the wrong scientific formula for the new products.

The Examiner's decision is reversed.

REVERSED

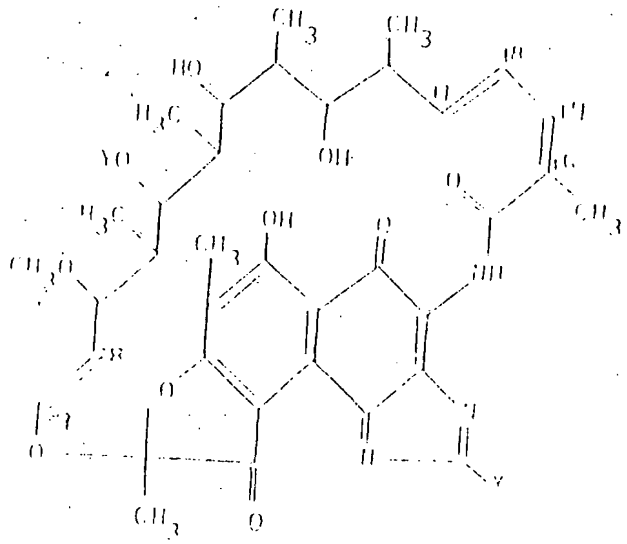
H. Nagel
Examiner-in-Chief)
)
Brereton)
)
Sturtevant) BOARD
Examiner-in-Chief) OF
) APPEALS
)
Eugene A. Lucchi)
Examiner-in-Chief)
(Acting))

Olson, Fisher, Spivak,
McClelland & Maier
Suite 400, 1755 S. Jefferson
Davis Highway
Arlington, VA 22202



(I)

wherein: X is a radical selected from the group comprising hydrogen, carboxyl, alkyl with less than 10 carbon atoms, cycloalkyl with less than 7 carbon atoms, alkenyl with less than 4 carbon atoms, cycloalkenyl with less than 7 carbon atoms, aryl hydrocarbon with less than 13 carbon atoms, aryl hydrocarbon-alkyl with less than 14 carbon atoms, aryl hydrocarbon-alkenyl with less than 11 carbon atoms, a heterocycle selected from the group comprising thiophene, furan, thiazole, tetrazole, thionaphthene, methylene dioxyphenyl, and pyridine, substitution products of the above specified radicals with a substituent which is at least one radical different therefrom and selected from the group comprising, in addition to all of the above specified radicals, halogen, hydroxyl, alkoxyl, nitro, amino, N-alkylamino, N,N-dialkylamino, formyl, carboxyl, carboalkoxy, carboxyalkoxy, N,N-dialkylaminoalkoxy, alkanoyloxy and acetamido, there being less than 14 carbon atoms in said radical X; Y is -H or $-COCH_3$, and its 16, 17, 18, 19 tetrahydroderivatives and 16, 17, 18, 19, 28, 29 hexahydroderivatives and corresponding oxidized products having the formula:



(II)

Exhibit A

WALLACE LABORATORIES

DIVISION OF CARTER-WALLACE, INC.

Cranbury New Jersey 08512

August 6, 1976

Mr. C. D. Houldsworth
Centre Europeen de Recherches Mauvernay
63, Riom
FRANCE

Dear Mr. Houldsworth:

We received from David Wilkins a method of synthesis for 14 C-labeled CERM 1978 and the non-labeled CERM 1978. These were both synthesized by the same method.

Our chemist, Dr. David Reisner, informs me that this method of synthesis can yield one of two possible products or a mixture of both products. He questions if CERM has any proof for their structural assignment either by physical measurements or by an unambiguous synthesis.

I would appreciate your transmitting to Dr. Busch the attached memoranda which clarify Dr. Reisner's specific questions.

Very truly yours,

H B Zimmerman Jr

H. B. Zimmerman
Vice President
Regulatory Affairs &
New Product Coordination

AMF/mf
Attachments

E.C.W. August 6, 1976

M E M O R A N D U M

TO: Mr. H. B. Zimmerman

FROM: D. B. Reisner, Ph.D.

DATE: June 30, 1976

SUBJECT: SYNTHESIS OF CERM 1978

The method of synthesis of ^{14}C-labeled CERM 1978 which accompanied Dr. Wilkins' letter of June 11, 1976, can conceivably yield a product which has a different chemical structure than the one assigned to CERM 1978 ^{14}C.

It is well-documented in the chemical literature that reactions of the type employed by CERM in Step 2 of their synthesis generally proceed <u>via</u> a cyclic "imonium" ion which can undergo cleavage at either one of the two carbon-to-nitrogen bonds of this intermediate. (See the attached reaction scheme). The product or products thus obtained would therefore depend upon the relative ease of splitting these two bonds.

In view of the fact that CERM's method of synthesis for 1978 ^{14}C is ambiguous, and since they are probably using the same method for preparing "cold" CERM 1978, we should determine if they have unequivocally established the identity of CERM 1978.

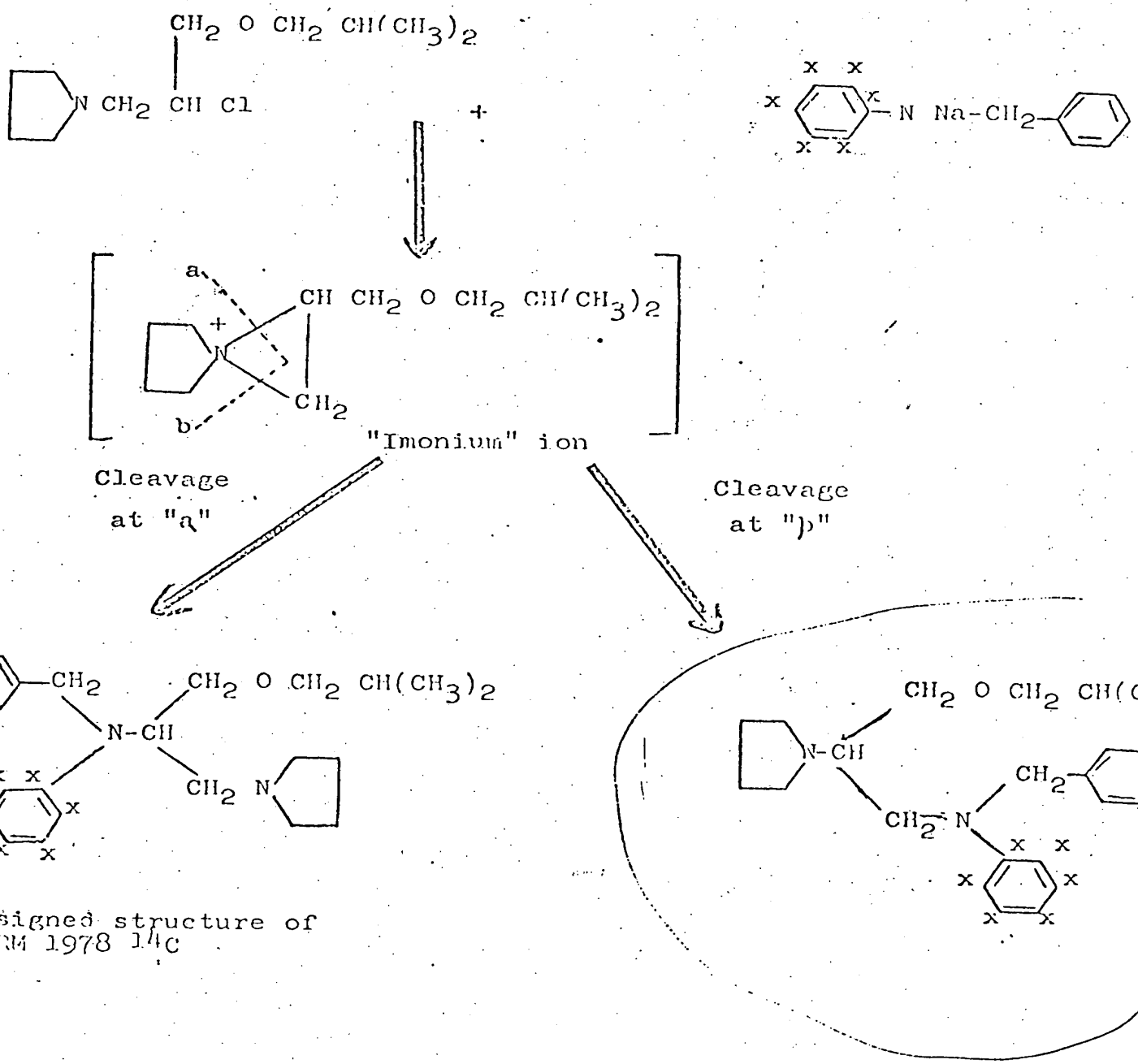
DBR

D. B. REISNER, PH.D.

DBR/lg

cc: N. Kucharczyk
R. D. Sofia
F. J. Stiefel

SYNTHESIS OF CERM 1978 ^{14}C



Assigned structure of
CERM 1978 ^{14}C

Exhib. F B

16.

UNIVERSITÉ DE PARIS VII
LABORATOIRE DE PHARMACOCHIMIE MOLÉCULAIRE

2, PLACE JUSSIEU, PARIS-V[e]
TÉL. : 3362525 POSTE : 6050

PARIS, LE 10 janvier 1977.

Monsieur N. BUSCH
Directeur Scientifique
CERM, route de Marsat
63201 RIOM.

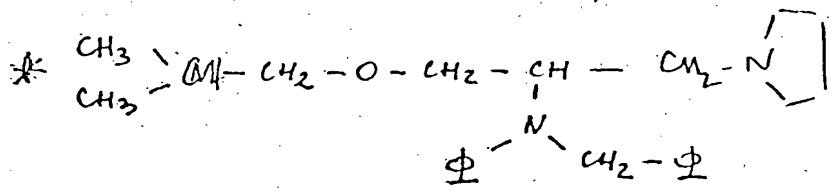
Monsieur R. MILCENT.

ETUDE PAR SPECTROMETRIE DE MASSE DES ECHANTILLONS:

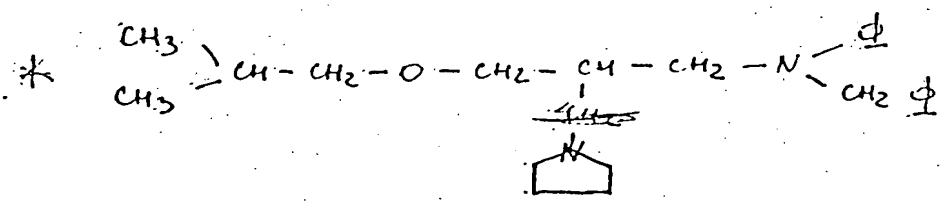
CERM 1

et CERM 2

Structure proposée pour $CERM_1$:



Structure proposée pour CERM 2:



Les deux spectres sont identiques dans leur ensemble, toutefois, le spectre de $CERM_2$ montre quelques pics supplémentaires d'assez grandes abondances; il s'agit de $\frac{m}{e}$: 290, 241,237,142 et des pics d'abondance supérieure à ceux du spectre de $CERM_1$ $\frac{m}{e}$: 222,210,208, 201.

Les premiers auxquels il n'a pas été possible d'attribuer une formule pourraient provenir d'une impureté contenue dans l'échantillon $CERM_2$ (coloré en jaune).

Les seconds demeurent inexpliqués si l'on n'accepte pas l'hypothèse d'une aberration expérimentale.

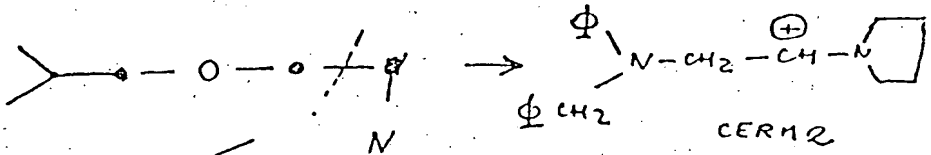
1ère conclusion: Les deux spectres correspondent à un seul et même produit.

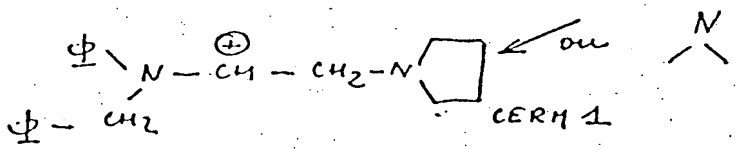
Etude de quelques pics de grandes abondances des deux spectres:

$\frac{m}{e}$: 366 : ion radical moléculaire.

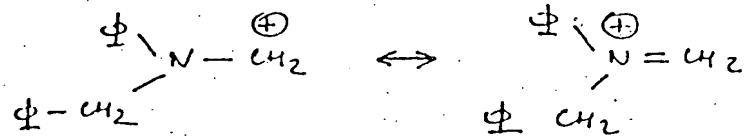
$\frac{m}{e}$: 362 : perte 1 à 1 de 4H dans la molécule.

$\frac{m}{e}$: 279 : rupture:

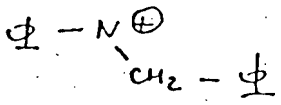




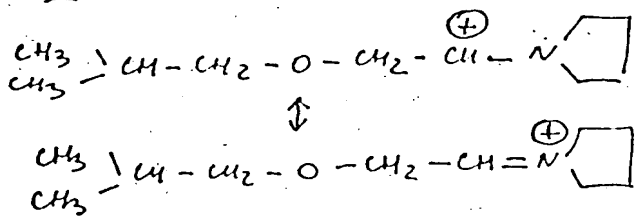
$\frac{m}{e}$: 196 : correspond à une autre rupture possible seulement pour la structure CERM2. dont l'ion formé est :



$\frac{m}{e}$: 182 :

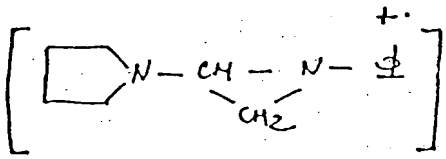


$\frac{m}{e}$: 170 : attribué à



caractéristique de la structure CERM2.

Si l'on ajoute le $\frac{m}{e}$: 199, de faible abondance qui peut être attribué à



les résultats obtenus permettent d'apporter une seconde conclusion:
la structure du produit est celle de CERM2.

Mes meilleurs vœux

4 Exhibit C

WALLACE LABORATORIES

DIVISION OF CARTER-WALLACE, INC.

Cranbury, New Jersey 08512

December 23, 1976

Mr. C. Houldsworth
Centre Europeen de Recherches Mauvernay
63, Riom
FRANCE

Dear Mr. Houldsworth:

In a letter dated August 6, 1976, Mr. Zimmerman informed you that we were concerned that the method of synthesis for CERM 1978 could yield one of two possible products or a mixture of both products. We questioned at that time if there was any proof for your structural assignment.

We have conducted numerous investigations relative to the structural assignment including mass spectroscopic and NMR data. Our data indicate a structure different from your assignment.

I would appreciate your transmitting the attached data to Dr. Busch for his comments. This matter is quite urgent, since we plan to file the Notice of Claimed Investigational Exemption (IND) by January 15, 1977.

Very truly yours,

Ana Fontana

Ana M. Fontana
Associate Director
Regulatory Affairs &
New Products Coordination

AMF/sfa

Attachments
cc: Dr. D. Reisner
Mr. H. B. Zimmerman

OFFICE MEMORANDUM

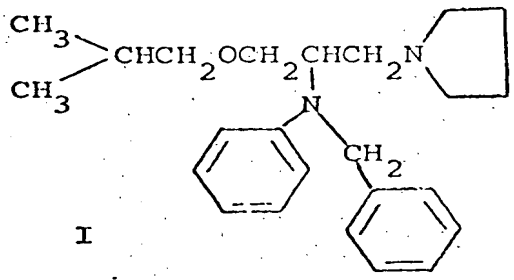
TO: Dr. D. B. Reisner

FROM: Mr. F. J. Stiefel

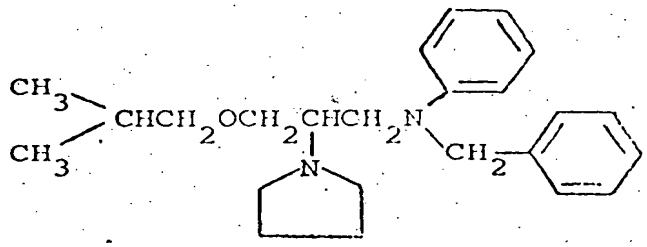
DATE: December 15, 1976

SUBJECT: Confirmation of the Structure for CERM's 1978 (W-2799M)

There has always been a doubt in this laboratory that the structure of CERM's 1978 was not I as submitted by CERM but rather II, a position isomer formed by rearrangement in the last step of the synthesis. (See DBR's memo to HBZ 6/30/76 and FJS to DBR 7/20/76).

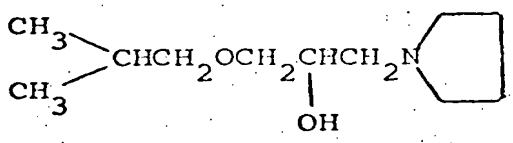


I

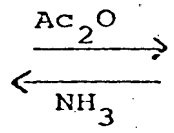


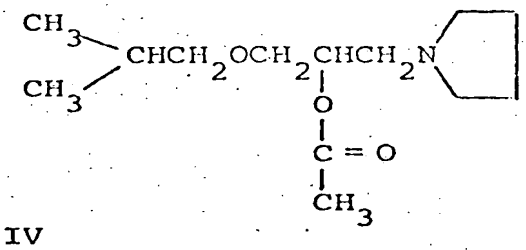
II

In order to confirm the structure as either I or II some additional chemistry has been done and the results show that II is the correct structure for CERM 1978.



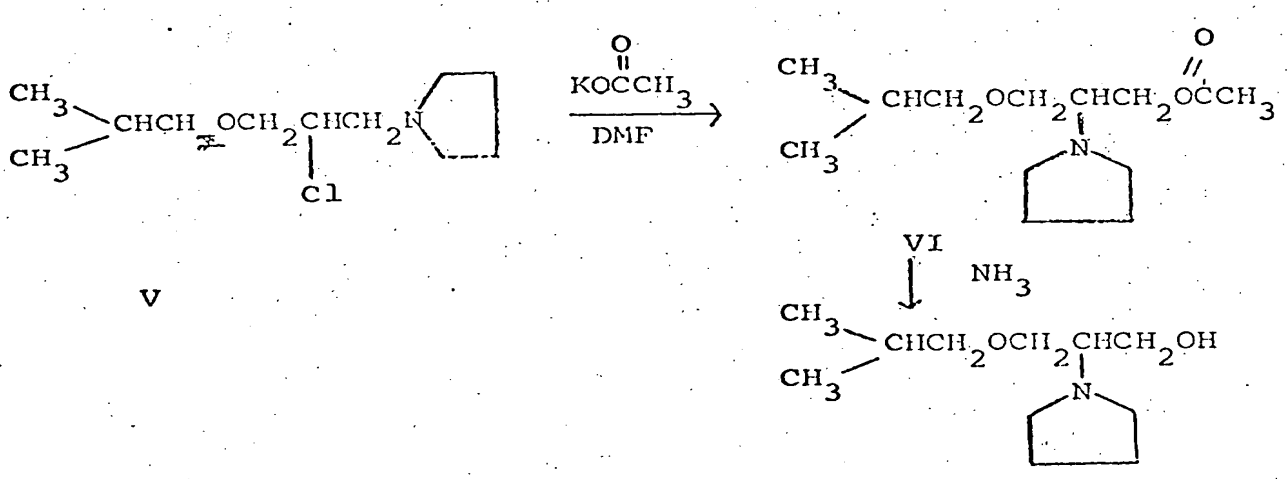
III





IV

The amino-alcohol III was acetylated with acetic anhydride and the product analysed by nmr. The spectra showed all the peaks as expected for Structure IV. Compound IV was hydrolysed with alcoholic ammonia and the product isolated was identical to III by nmr. This shows that there is no rearrangement of the molecule by this reaction.



V

VII

In another experiment the chloramine V, the precursor to CERM's 1978, was reacted with potassium acetate in DMF. Now if we are to believe the people at CERM, this reaction would be a simple displacement of the chlorine atom with acetate to give known IV. However, the acetate that was isolated did not correspond to IV by nmr but the peaks indicated VI to be the structure only obtainable via a rearrangement. Compound VI was hydrolysed with alcoholic ammonia and gave an amino-alcohol VII different than III. If the reaction of potassium acetate with chloramine III gives a rearranged product so also will the reaction of N-benzyl aniline and in fact will produce the isomer II.

Recently a sample of W-2799M (RC-754) was sent to Shrader Laboratories for High Resolution MS. The results of this analysis corroborates the assignment of the structure to isomer II, (see attachment). There is no other arrangement of the molecule that would give a 100% peak of mass 170 than that of Structure II.

This new information should be conveyed to Dr. Kucharczyk so that he will be aware of the possible metabolites from the compound based on this new structure.

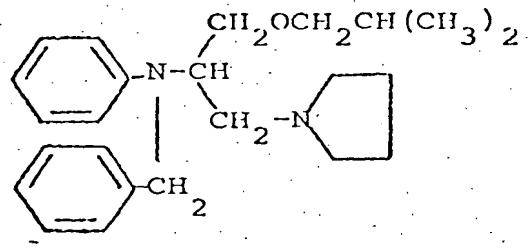
F. J. Stiefel

FJS/mf

cc: Dr. Kucharczyk
Dr. Sofia
Mr. Zimmerman

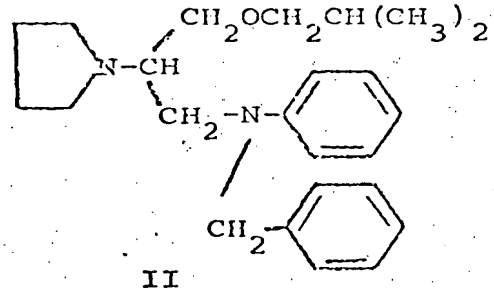
C.W 23.12.1976

The structure shown below as Structure I for CERM 1978 was assigned by the CERM chemists. We at Carter-Wallace investigated the structure for this compound and have obtained evidence, i.e. NMR and Mass Spectroscopic Data, that supports Structure II.



I

1-[2-(N-Benzylanilino)-3-isobutoxypropyl]pyrrolidine

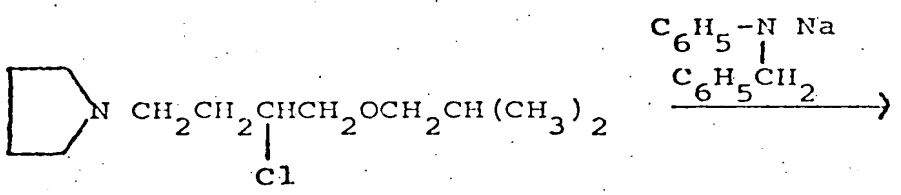


II

N-Benzyl-N-(3-isobutoxy-2-pyrrolidinopropyl)aniline

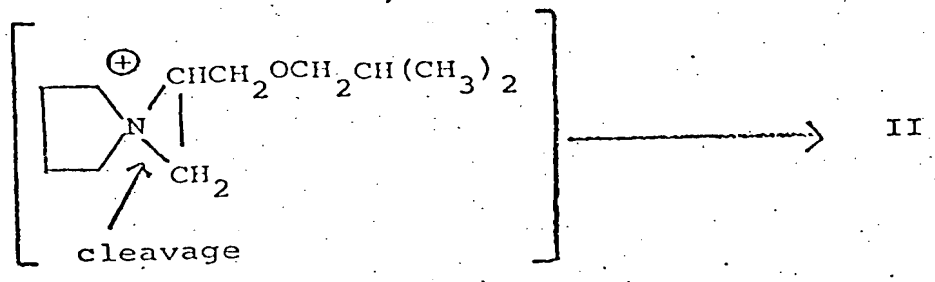
In addition to employing instrumental methods to determine the structure of CERM 1978, we studied the chemical properties of a key intermediate, 1-(2-chloro-3-isobutoxypropyl)pyrrolidine, 1, which can conceivably form a cyclic "immonium" ion 2 (Chart I) that can then undergo cleavage in the presence of the sodium salt of benzylaniline in the synthesis of CERM 1978 to yield a product having Structure II.

CHART I



1

CHART I (Cont'd)



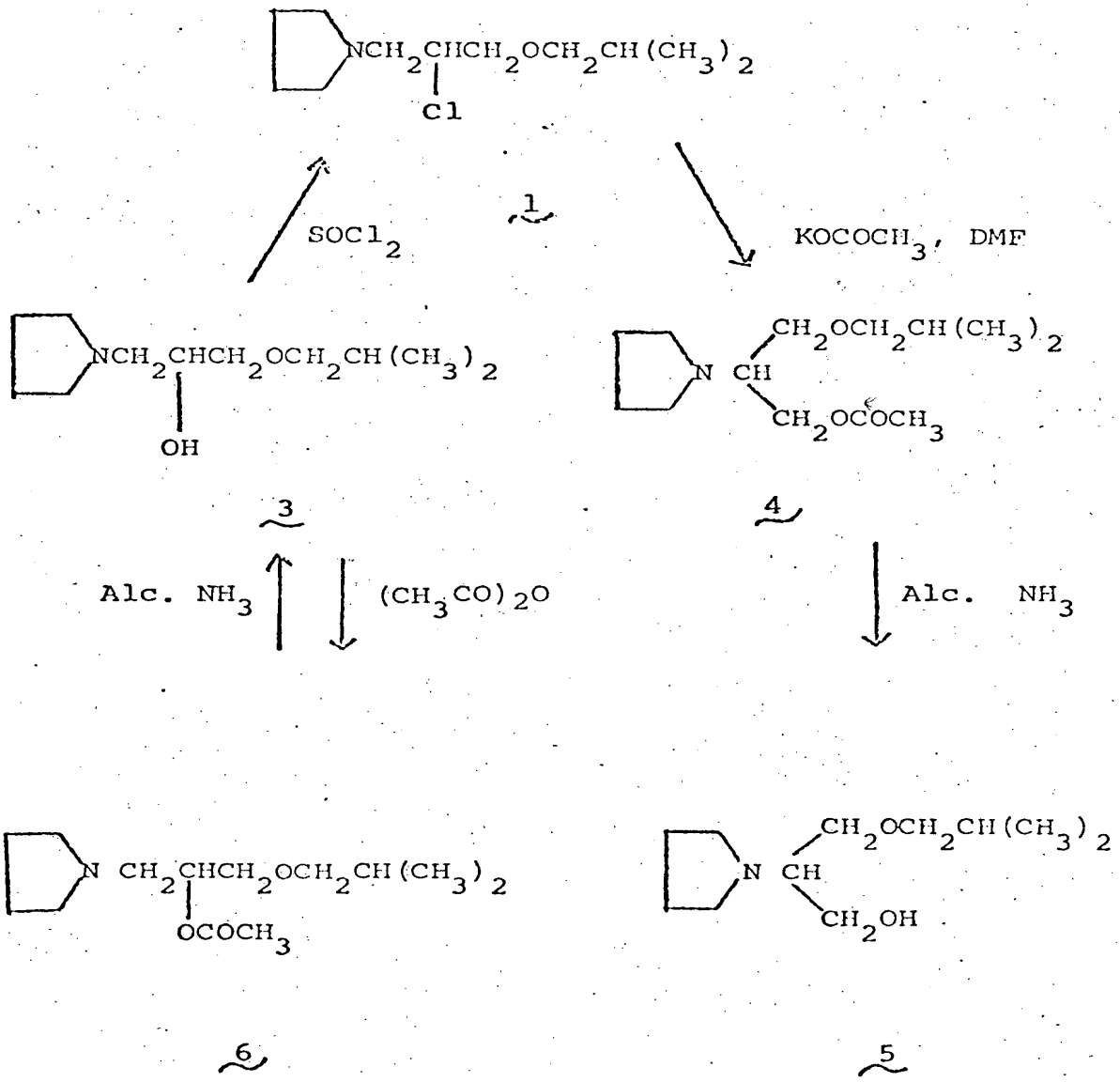
"Immonium" ion 2

II

We found that the same key intermediate 1, which is obtained from 1-(2-hydroxy-3-isobutoxypropyl)pyrrolidine, 3, does indeed undergo a rearrangement to yield an alcohol 5, different from alcohol 3, when treated with potassium acetate in DMF and the resulting acetate 4 is hydrolyzed with alcoholic ammonia (Chart II). Also, it was shown that the acetate 4 is different from the acetate 6 which was prepared by acetylation of 3 with acetic anhydride. Furthermore, the acetate 6 was hydrolyzed by the method used to hydrolyze 4 and the expected alcohol 3 was obtained.

We are now in communication with CERM regarding our findings and structural assignment for CERM 1978. At the same time, we are continuing our investigations relative to the structure of this compound.

CHART II


NCH2CHCH2OCH2CH(CH3)2
Cl
1
SOCl2
KOCOCH3, DMF
NCH2CHCH2OCH2CH(CH3)2
OH
3
N CH
CH2OCH2CH(CH3)2
CH2OCOCH3
4
Alc. NH3
(CH3CO)2O
Alc. NH3
N CH2CHCH2OCH2CH(CH3)2
OCOCH3
6
N CH
CH2OCH2CH(CH3)2
CH2OH
5

Exh 31F B

Shrader Analytical & CONSULTING LABORATORIES, INC.
MASS SPECTROMETRY, GAS CHROMATOGRAPHY, ELEMENTAL ANALYSES

3450 LOVETT AVENUE • DETROIT, MICHIGAN 48210

894-4440
894-4441

December 8, 1976

ANALYTICAL RESULTS

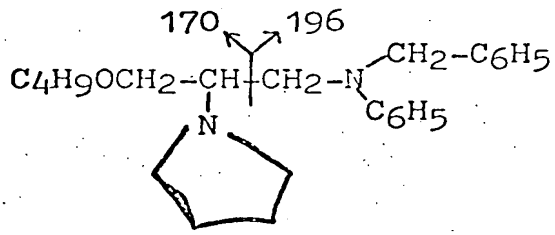
CUSTOMER : Carter-Wallace

SAMPLE NO. : RC-754

ANALYSIS : High resolution MS

RESULTS : HR2662A

A weak molecular ion at m/e 366.2620 confirms the expected composition $C_{24}H_{34}ON_2$. The fragments at m/e 196 ($C_{14}H_{14}N$) and 170 ($C_{10}H_{20}ON$) indicate that the compound has structure II.



II

Stephen Shrader - Ph.D.

SHRADER ANALYTICAL
& CONSULTING LABORATORIES, INC
DETROIT MICHIGAN 48210

CARTER-WALLACE RC-794
PROBE GOLD
11/30/76

MR2662A

1 1

CALCULATED MASS	DEV	C12/13	H	O	N	MEASURED MASS	NO. PTS	REL INT
366.2670	-4.9	24/0	34	1	2	366.2620	15	.2
279.1860	3.2	19/0	22	0	2	279.1882	20	.4
208.1125	3.0	15/0	14	0	1	208.1156	9	.1
NO COMP CALC						198.1251	6	.1
197.1204	- .9	14/0	15	0	1	197.1195	33	1.5
196.1126	.5	14/0	14	0	1	196.1130	42	3.5
195.1047	-1.3	14/0	13	0	1	195.1033	8	.1
NO COMP CALC						194.0934	10	.1
187.1234	- .2	12/0	15	0	2	187.1232	18	.4
183.1047	- .8	13/0	13	0	1	183.1040	29	.7
182.0969	- .5	13/0	12	0	1	182.0964	13	.2
181.0891	.1	13/0	11	0	1	181.0882	19	.3
180.0813	1	13/0	10	0	1	180.0814	16	.3
NO COMP CALC						172.1617	25	.7
NO COMP CALC						171.1574	63	11.1
NO COMP CALC						170.2129	18	.2
170.1544	- .1	10/0	20	1	1	170.1544	98	100.0
170.0843	-1.6	11/0	10	0	2	170.0827	8	.1
NO COMP CALC						170.0671	5	.1
169.1465	.1	10/0	19	1	1	169.1467	42	4.7
168.1388	- .8	10/0	18	1	1	168.1380	37	2.2
NO COMP CALC						139.5942	9	.2
132.0813	1.5	9/0	10	0	1	132.0827	12	.1
NO COMP CALC						131.0175	5	.1

1 2

CALCULATED MASS	DEV	C12/13	H	O	N	MEASURED MASS	NO. PTS	REL INT
130.0656	1.1	9/0	8	0	1	130.0667	15	.2
126.0918	-.3	7/0	12	1	1	126.0915	14	.2
NO COMP CALC						124.1167	15	.2
120.0813	.8	8/0	10	0	1	120.0821	33	1.3
119.0734	.4	8/0	9	0	1	119.0738	12	.2
118.0656	1.8	8/0	8	0	1	118.0675	29	.5
NO COMP CALC						115.0944	21	.6
114.0918	-.3	6/0	12	1	1	114.0915	56	11.2
113.0840	-1.2	6/0	11	1	1	113.0828	40	2.4
112.0762	-1.0	6/0	10	1	1	112.0751	49	8.4
NO COMP CALC						111.1090	9	.1
111.1047	-1.3	7/0	13	0	1	111.1035	6	.1
110.0969	1.2	7/0	12	0	1	110.0981	9	.1
110.0605	2.8	6/0	8	1	1	110.0633	7	.1
106.0656	-.6	7/0	8	0	1	106.0650	37	1.6
105.0579	.2	7/0	7	0	1	105.0579	43	3.6
104.0499	.5	7/0	6	0	1	104.0505	39	3.3
NO COMP CALC						99.0999	6	.1
98.0969	-.6	6/0	12	0	1	98.0963	49	4.1
97.1017	2.4	7/0	13	0	0	97.1041	9	.1
97.0891	-.1	6/0	11	0	1	97.0889	43	2.0
96.0813	1.2	6/0	10	0	1	96.0825	41	2.7
NO COMP CALC						96.0401	8	.1
94.0656	2.7	6/0	8	0	1	94.0683	8	.1

1.3

CALCULATED MASS	DEV	C12/13	H	O	N	MEASURED MASS	NO. PTS	REL INT
93.0578	1.7	6/0	7	0	1	93.0595	29	.5
92.0625	-2.8	7/0	8	0	0	92.0598	43	2.2
91.0547	.3	7/0	7	0	0	91.0550	54	18.8
90.0469	.9	7/0	6	0	0	90.0478	22	.4
89.0391	-.1	7/0	5	0	0	89.0390	19	.3
85.0891	-.7	5/0	11	0	1	85.0883	6	.1
84.0813	1.3	5/0	10	0	1	84.0826	61	4.4
83.0860	.6	6/0	11	0	0	83.0866	5	.1
83.0734	1.2	5/0	9	0	1	83.0747	20	.5
82.0782	2.6	6/0	10	0	0	82.0803	5	.1
82.0782	-1.0	6/0	10	0	0	82.0772	5	.1
82.0656	.0	5/0	8	0	1	82.0656	18	.2
78.0469	.9	6/0	6	0	0	78.0478	38	.7
77.0391	1.5	6/0	5	0	0	77.0406	80	4.0
77.0265	.3	5/0	3	0	1	77.0268	6	.1
74.0156	-2.1	6/0	2	0	0	74.0135	5	.1
NO COMP CALC						73.0285	7	.1
72.0813	.6	4/0	10	0	1	72.0819	6	.1
NO COMP CALC						72.0490	7	.1
72.0449	-.9	3/0	6	1	1	72.0440	14	.2
71.0860	2.1	5/0	11	0	0	71.0881	12	.1
NO COMP CALC						71.0827	5	.1
71.0734	-.9	4/0	9	0	1	71.0726	15	.2
70.0656	.9	4/0	8	0	1	70.0665	36	1.0

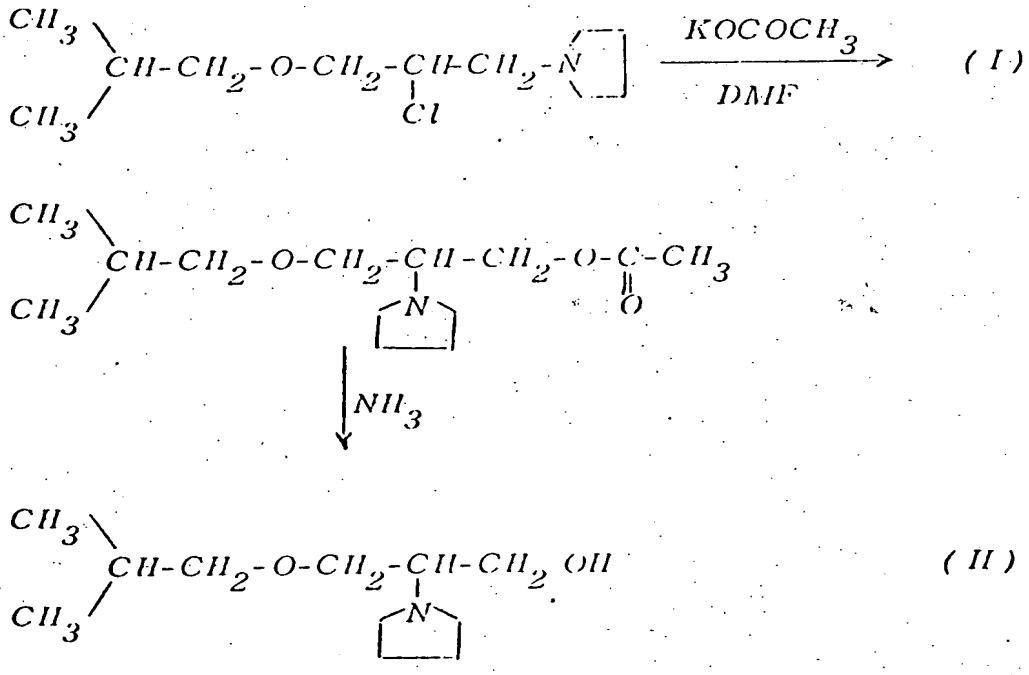
CALCULATED MASS	DEV	C12/13	H	O	N	MEASURED MASS	NO PTS	REL INT
NO COMP CALC						70.0577	6	.1
70.0292	- .8	3/0	4	1	1	70.0284	16	.2
69.0704	1.6	5/0	9	0	0	69.0720	5	.1
69.0578	.4	4/0	7	0	1	69.0582	56	1.5
NO COMP CALC						68.0468	16	.3
NO COMP CALC						67.0516	7	.1
NO COMP CALC						67.0483	9	.1
LIMIT OF DATA								

Exhibit E

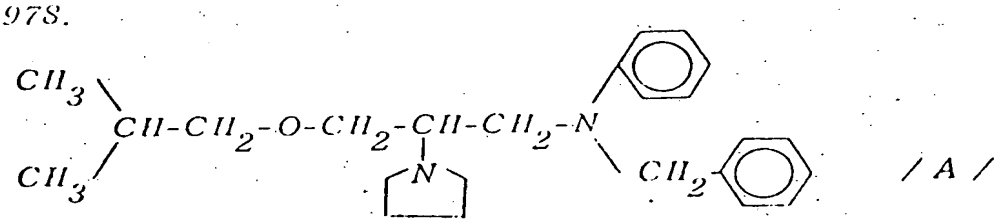
Comments by Dr. BUSCH to C.W.'s letter concerning the structure of CERM 1978 (AMF/sfa December 23, 1976)

A - Chemical data submitted by C.W.

When the chloramine(I)is allowed to react with potassium acetate and after treatment of the ester obtained with ammonia, the product isolated is the amino alcool(II.)

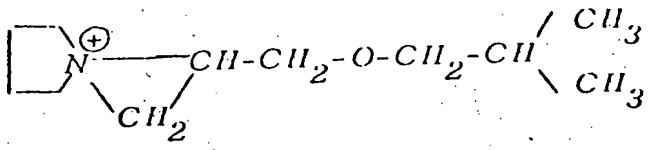


From this result, C.W.'s chemists deduce that the synthetic method developed at CERM leads to a compound with structure(A), a position isomer of 1978.



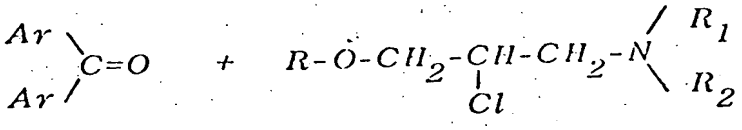
This conclusion however proceeds from experimental conditions which are not similar to those used in 1978 preparation.

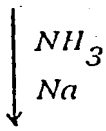
When we started our researches with chloramines of type I, we considered the possibilities of immonium ion(III) attack.

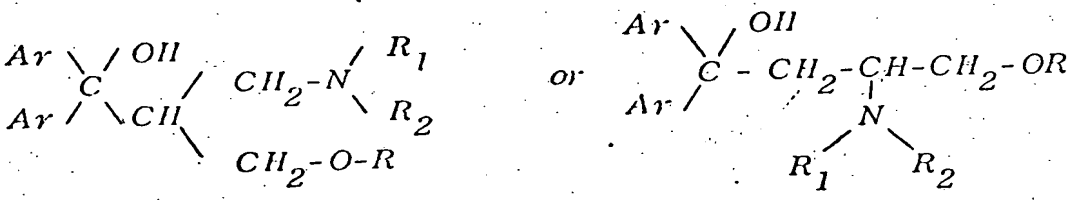


(III)

1/ - The first series of compounds derivated from chloramines(I) were obtained by the following reaction schema



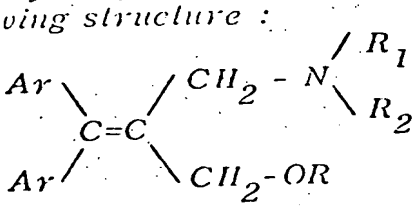




(IV) (V)

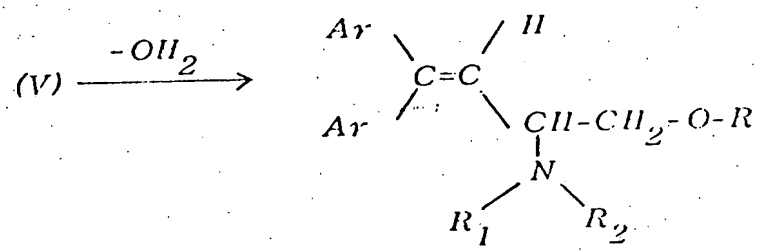
which could yield either(IV) or(V).

By dehydration of the products, we were in a position to establish the following structure :



(VI)

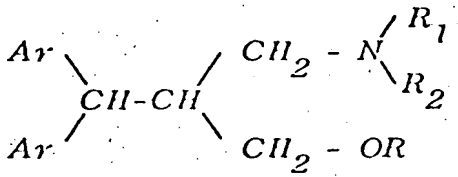
since RMN spectra did not show the ethylenic proton which would have been present had the type(V)structures been obtained



(VII)

This led us to assign the structure IV to the above mentioned amino-alcools.

2/ - When the type I chloramines are allowed to react with Sodium-diphenyl methane in THF, compounds of type (VIII) are obtained.



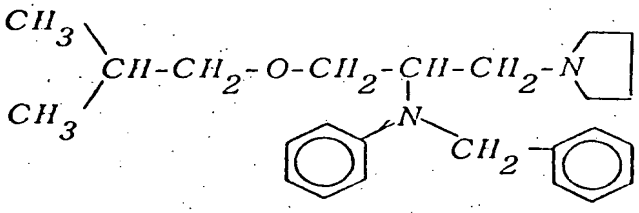
(VIII)

These are similar to those resulting from catalytic hydrogenation of type (VI) compounds.

Remark

In every case, type 1 and 2 reactions have led to unique compounds not to mixtures of isomers. Such mixtures are indeed obtained when type I chloramines are allowed to react with sodium derivatives of benzonitrile or diethylmalonate.

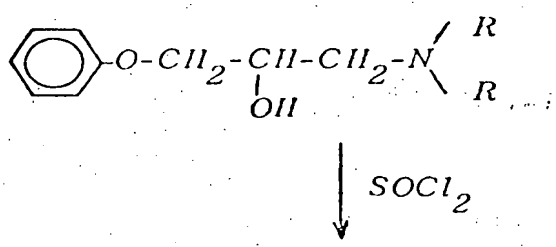
These data and the fact that RMN and IR spectra were in agreement with the structure envisaged for CERM 1978 have led us to consider that we were indeed dealing with the compound of structure :

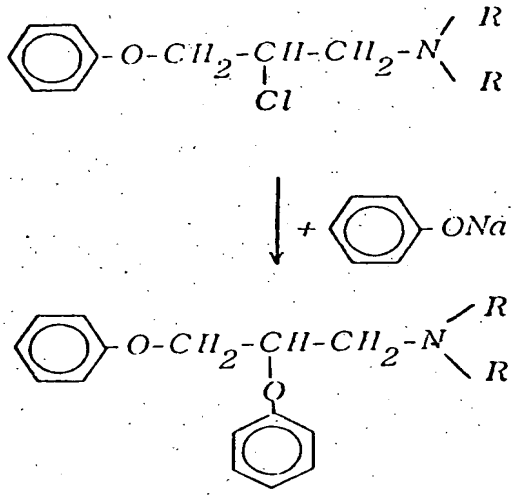


In addition, several published works describe the reactions of type (I) chloramines.

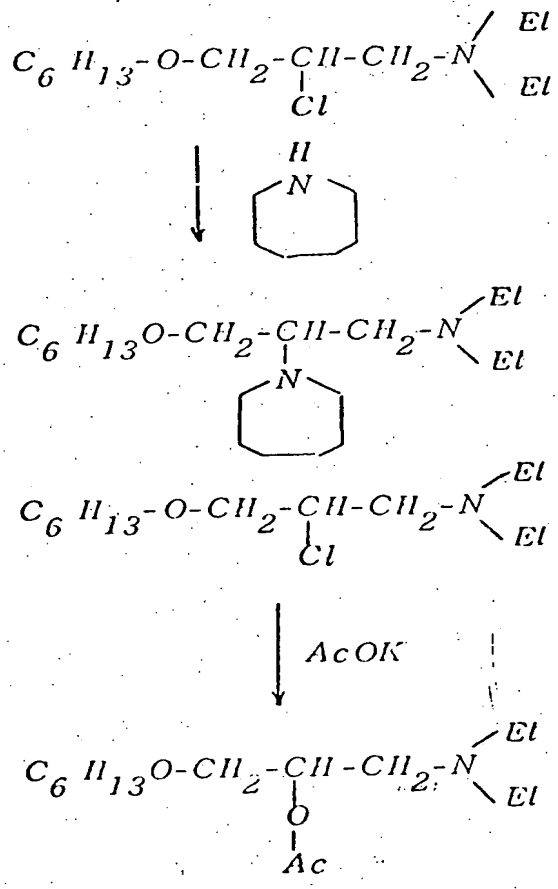
a) Synthesis of new aryloxy derivatives of N-substituted propylamines.

V. Danksas, G. Pikunaite
Zh. Vses. Khim. Obshestsva 9 (3), 352-354, 1964



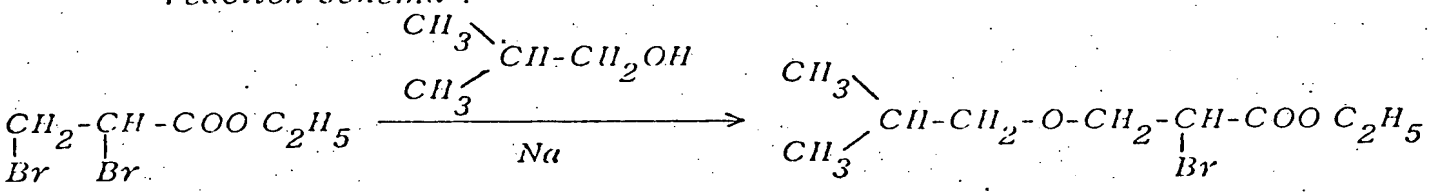


b) S. Mamedov and al.
Zh. Organ. Khim., 2 (8), p. 1377-1382, 1966 - C.A. 66 54966

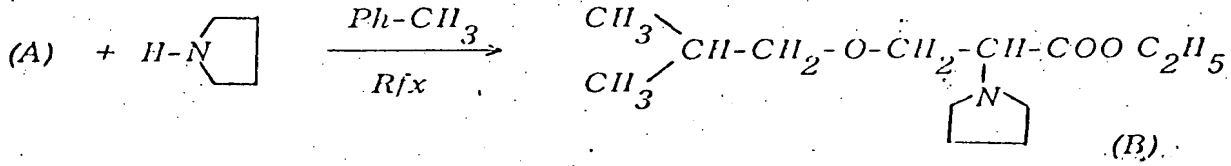


2/ - Research of an unambiguous synthetic preparation of type IX structure

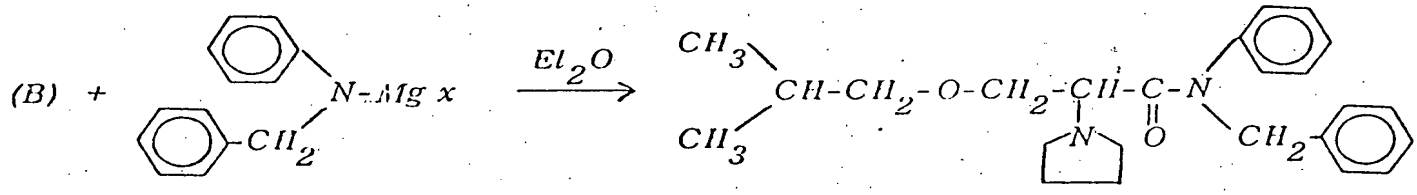
Type IX structure has been obtained through the following reaction schema :



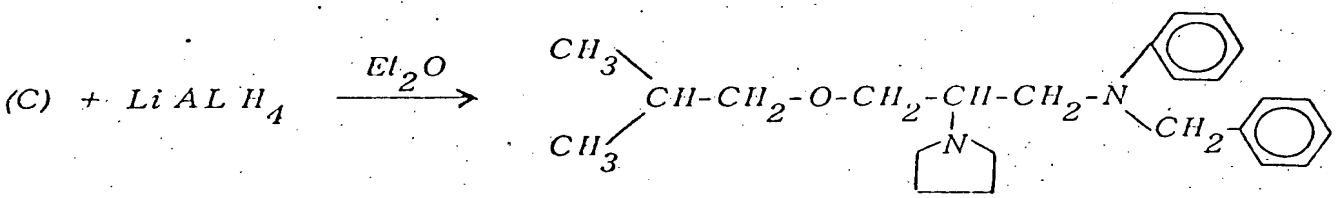
(A)



(B)



(C)

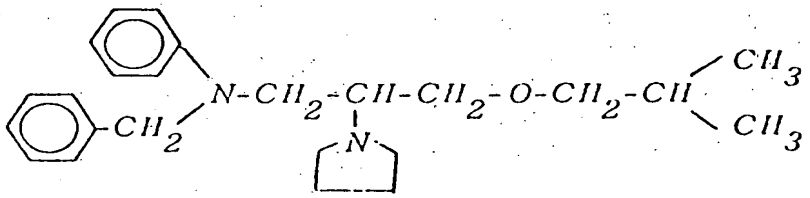


(D)

Compound D obtained has the same physicochemical characters than CERM 1978.

Conclusion

The chemical structure assigned to CERM 1978 is :

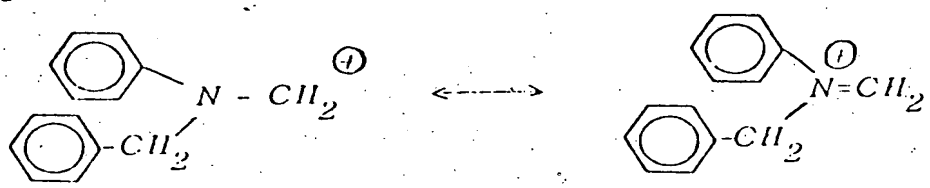


B - Confirmation of the structure for 1978 CERM

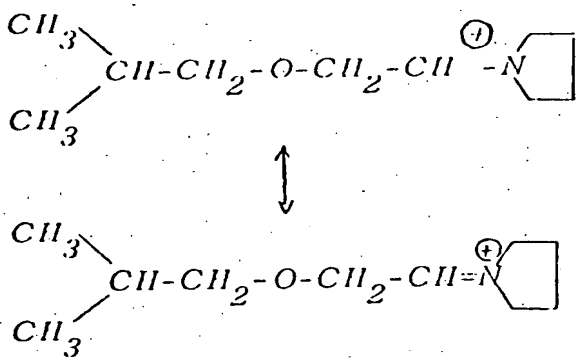
1/ - Mass spectrometry

Studies conducted at Paris University VII have shown among others two fragments :

a)- $\frac{m}{e} = 196$



b)- $\frac{m}{e} = 170$



which can result only from the structure

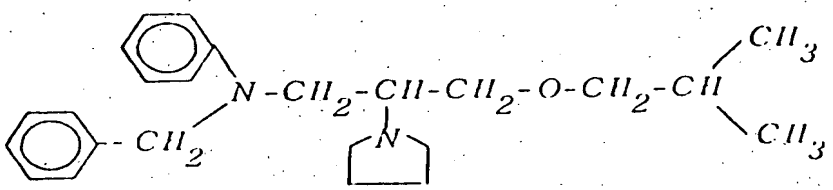


Exhibit F

UNIVERSITÉ DE PARIS VII
LABORATOIRE DE PHARMACOCHIMIE MOLÉCULAIRE

2, PLACE JUSSIEU, PARIS-Vᵉ
TÉL. : 3362525 POSTE : 6050

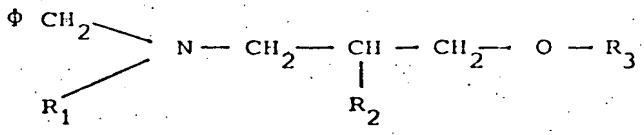
Réf. JJG/AM 56.

PARIS, LE 11 juillet 1977

Monsieur N. BUSCH
C.E.R.M.
Route de Marsat
63201 RIOM.

SPECTRES DE MASSE DES ECHANTILLONS
N°S 1979, 1991, 3012, 3080,

De structure générale:



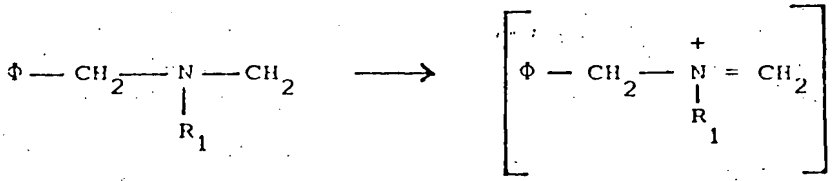
1) Pics moléculaires:

1979: faible M^+ (367) et impureté à M = 391
1991: M^+ inexistant (368), mais présence d'un pic à M = 372
3012: faible M^+ (324)
3080: moyen M^+ (382)

La faible importance de ces pics et l'inexistence pour 1991, montre la fragilité des molécules proposées (source: 150°C; énergie: 70eV). La présence de pic de haute masse supplémentaire est due à des impuretés.

2) Fragmentations:

La plus importante fragmentation, qui fournit le pic de base dans plusieurs cas, est le retrait de:



(1979, 1991).

Une fragmentation symétrique à la première est remarquée, qui correspond à la perte de:

$$CH_2 - O - R_3 \longrightarrow CH_2 = \overset{+}{O} - R_3$$

(1979,1991, 3080).

Enfin, le 3ème type de fragmentation correspond à la perte de:

$$R_2 - CH - CH_2 - O - R_3 \longrightarrow R_2 - \overset{+}{C}H - CH_2 - O - R_3$$

(3012, 3080).

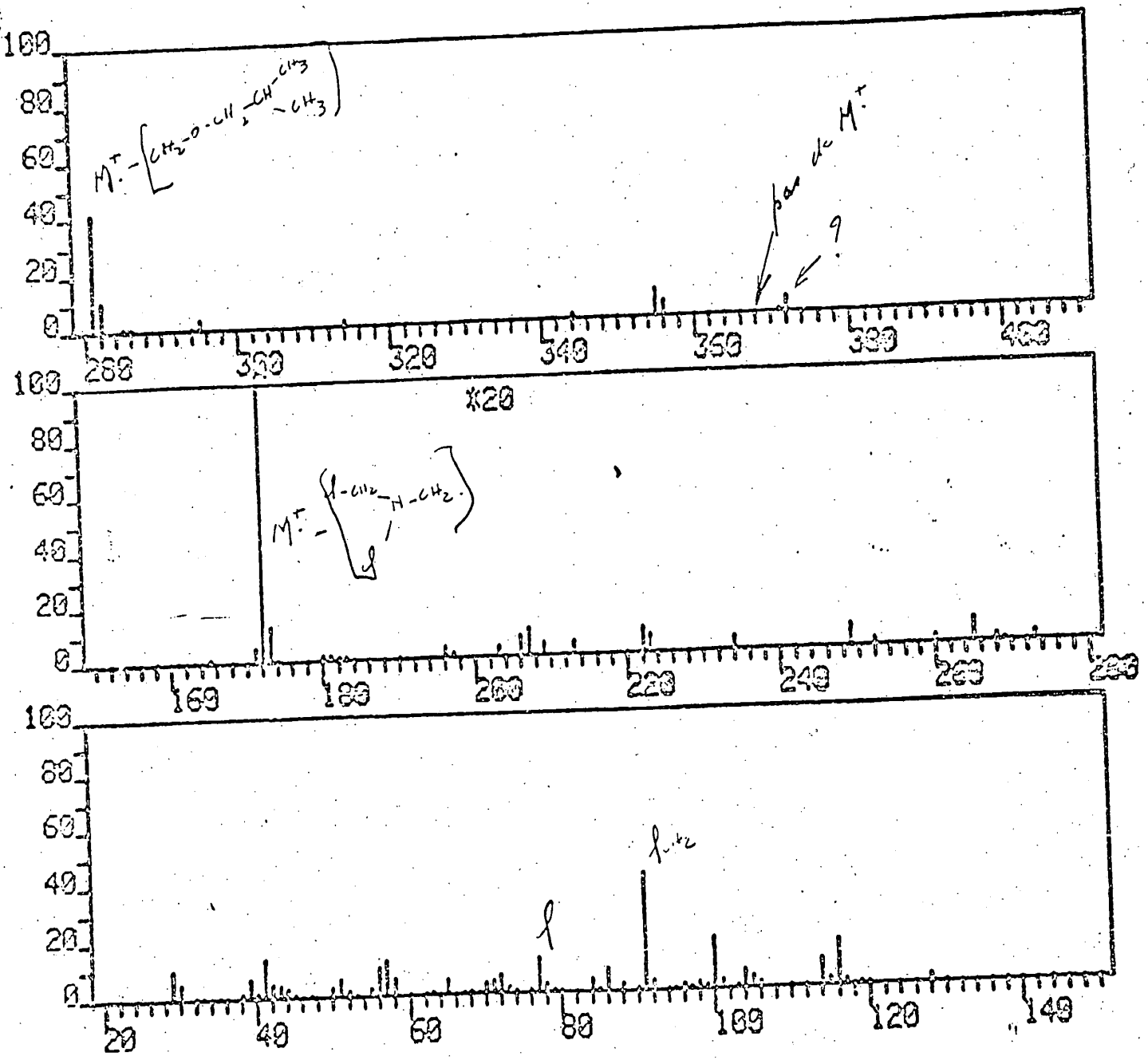
Ensuite, on remarque très normallement la dégradation des différents groupements.

pour R. MILCENT.

J.J. GODFROID.

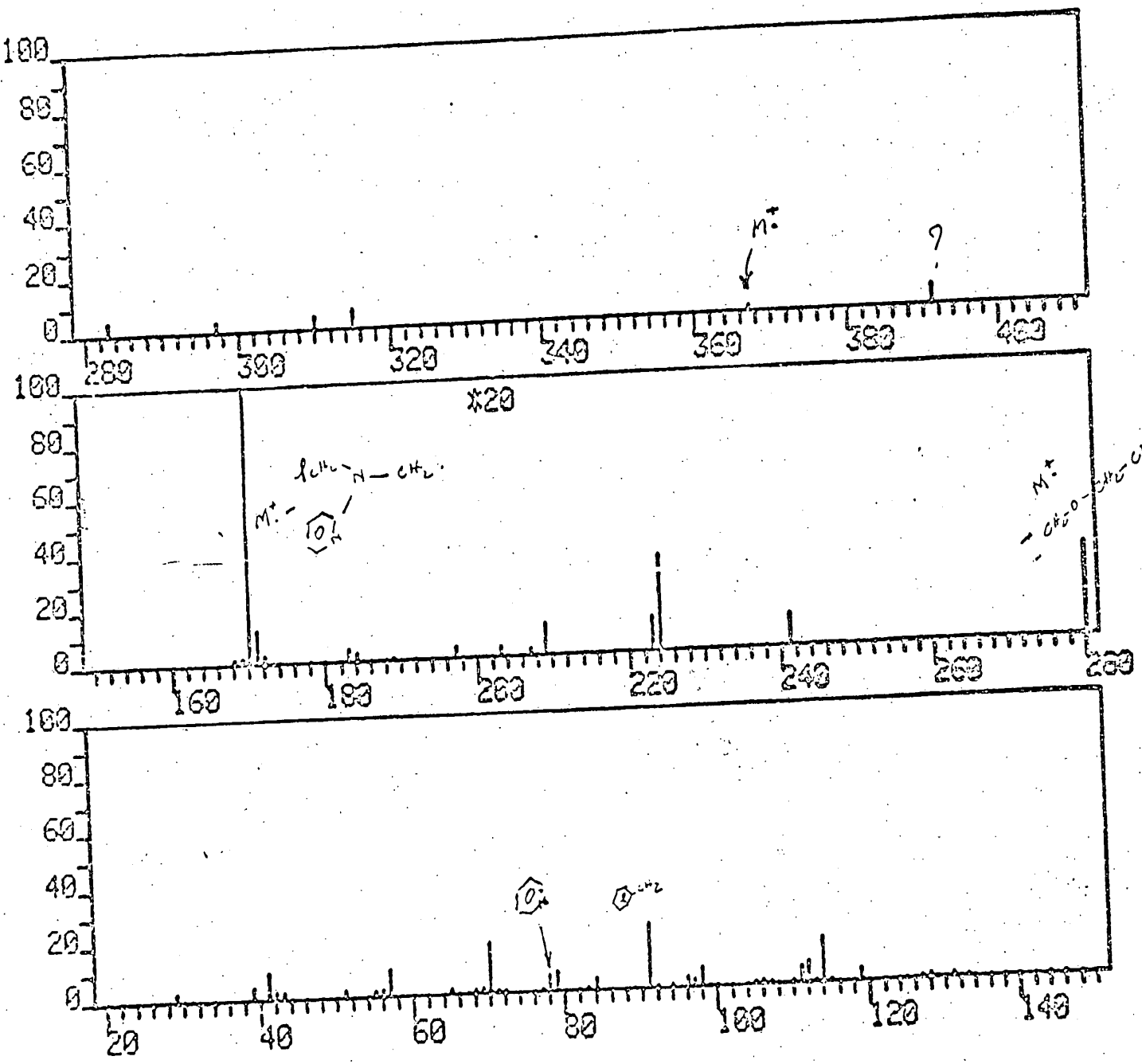
DS-50 MASS INTENSITY REPORT:

2730



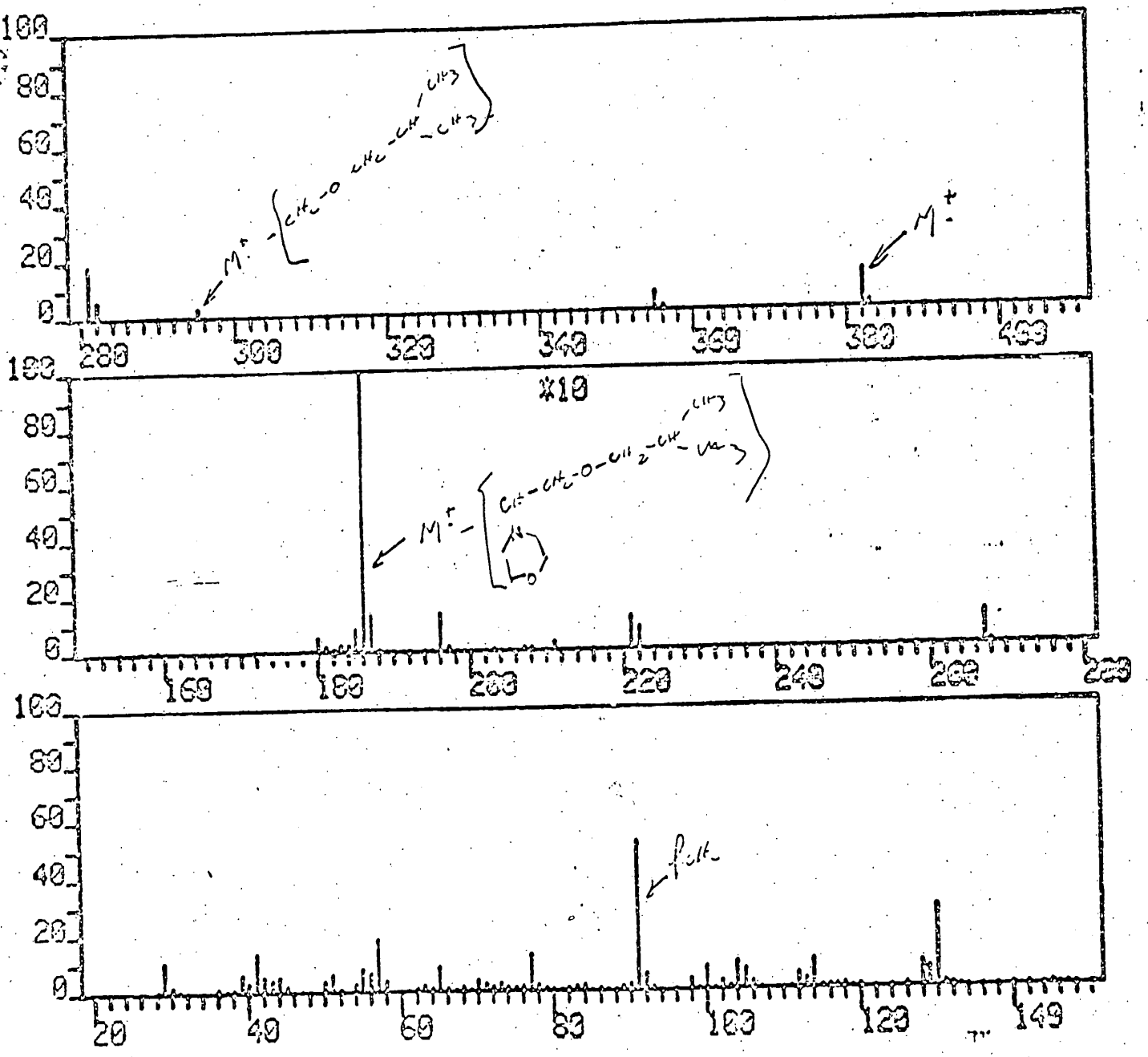
DS-50 MASS INTENSITY REPORT: 9E.44 [TIC=8973, 100%=2653]

-273



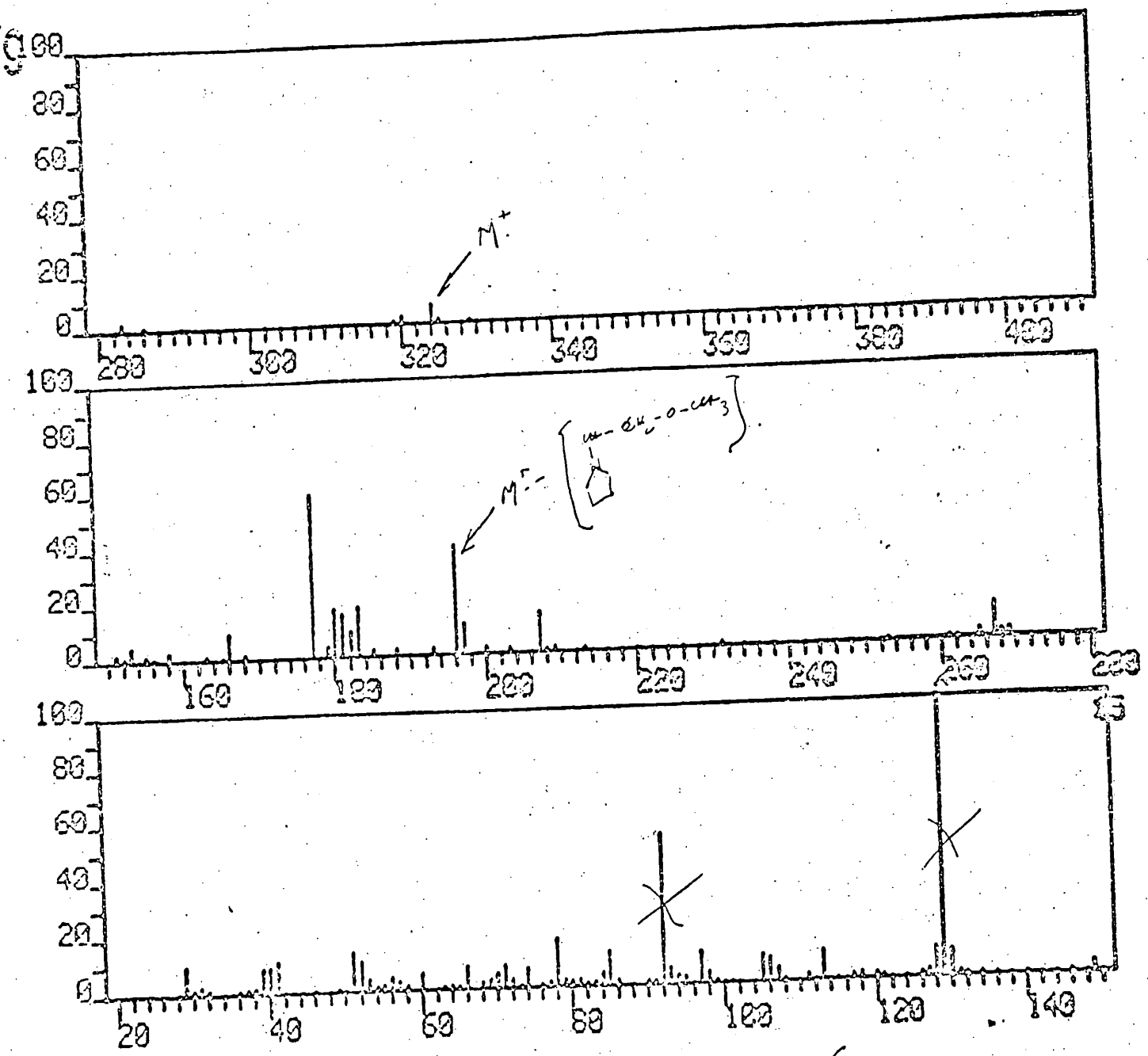
DS-50 MASS INTENSITY REPORT: 9A.48 [TIC=5R106, 100%=9633]

2720



DS-50 MASS INTENSITY REPORT

272



réarrangements possibles